PERGAMON

European Journal of Cancer 38 (2002) 1365–1377

European Journal of Cancer

www.ejconline.com

Paediatric Update

Emergencies and their management

G. Nicolin*,[1]

University of Oxford, Department of Paediatric Haematology and Oncology, Level 4, John Radcliffe Hospital, Headington, Oxford OX3 9DU, UK

Received 17 January 2001; received in revised form 12 February 2002; accepted 19 February 2002

1. Introduction

The prognosis for children with cancer has improved steadily over the last few decades so that overall approximately 70% will now be cured. Part of this improvement has been due to more effective treatment regimens, but also increasing expertise in handling the severe life-threatening situations that are a complication of the malignancy itself or its treatment. There are, however, a number of unfortunate children who die not from the inherent resistance of the malignancy to treatment, but from complications, which if predicted and prevented or handled quickly and effectively would decrease morbidity and mortality. All practitioners who refer a child with suspected malignancy or who work in the specialty units must be able to recognise potential life-threatening emergencies and manage them appropriately.

Table 1 lists some of the emergencies that may be encountered during paediatric oncology practice.

It is beyond the scope of this article to discuss every possible urgent clinical problem that a child with a malignancy might develop. Many such problems are common to other paediatric patients and can be managed using established guidelines. Management of infections and the rational use of antibiotics will be covered in a later article in this Update series. This article will focus on the incidence, mechanisms and best current practice of the six emergencies most likely to arise in a child with cancer.

2. Metabolic problems

2.1. Tumour lysis syndrome

Tumour lysis syndrome comprises a number of metabolic abnormalities that occur as a result of spontaneous or treatment-related tumour cell death. This cytolysis releases large amounts of uric acid, phosphate, other purine metabolites and potassium into the circulation, which may lead to hypocalcaemia, precipitation of calcium phosphate and/or urate and ultimately acute renal failure. Tumour lysis syndrome has a high morbidity and some cases progress to multi-organ failure and death. It is a true emergency but if anticipated, may be prevented or treated before life-threatening complications develop.

The most commonly associated malignancies are the very chemosensitive B-cell and T-cell non-Hodgkin's lymphoma and T-cell acute lymphoblastic leukaemia (ALL). Both are often associated with large bulk solid disease or high white blood cell counts. Tumour lysis syndrome may also occur in acute myeloid leukaemia and non-high count acute lymphoblastic leukaemia and has occasionally been reported with other childhood malignancies including neuroblastoma, hepatoblastoma, hepatocellular carcinoma, sacrococcygeal teratoma, metastatic rhabdomyosarcoma and haemophagocytic lymphohistiocytosis. The syndrome may occur spontaneously, but usually develops within the 5 days after starting treatment. It is usually triggered by the administration of chemotherapy, but it has also been described after radiotherapy, embolisation and even surgery alone. A number of features at presentation suggest a higher risk of developing tumour lysis syndrome, as follows: presence of bulky abdominal disease; elevated pre-treatment plasma uric acid and lactate dehydrogenase (LDH); and decreased urine output [1–3].

* Tel.: +44-1865-221-066; fax: +44-1865-221-083.
E-mail address: gary.nicolin@paediatrics.oxford.ac.uk
[1] Clinical lecturer.

PII: S0959-8049(02)00072-2

Table 1
Paediatric oncological emergencies

Infections
○ Septicaemic shock
○ Interstitial pneumonitis
Metabolic problems
○ Tumour lysis syndrome[a]
○ Hypercalcaemia[a]
Haematological problems
○ Hyperleucocytosis[a]
○ Coagulopathy[a]
○ Acute haemorrhage
Space-occupying tumour problems
○ Superior vena cava syndrome/obstruction[a]
○ Spinal cord compression[a]
○ Raised intracranial pressure
○ Massive organomegaly
Other problems
○ Acute hypertension
○ Seizures
○ Acute anaphylaxis

[a] Problems dealt with in this article.

2.1.1. Pathogenesis of the clinical problems of tumour lysis syndrome

Hyperkalaemia is the most rapidly hazardous consequence of tumour lysis syndrome, although with conventional hydration and acid-base management its incidence is low [4]. Serum potassium rises because of its release from dying cells and may quickly reach dangerous levels if there is co-existing acute renal failure.

Hyperuricaemia is the single most common finding in patients with tumour lysis syndrome and acute renal failure [2]. Uric acid is derived from the catabolism of purines released from the nuclei of dying cells. The metabolic pathway is illustrated in Fig. 1. In the presence of hyperuricaemia, renal uric acid excretion increases. However, this increased urinary uric acid clearance occurs in patients with non-Hodgkin's lymphoma (NHL) and ALL, even if their plasma uric acid levels are normal, and is independent of the glomerular filtration rate [5]. It is likely that it is the urinary level rather than the plasma level of uric acid that is important in the pathogenesis of urate nephropathy. Uric acid, which is soluble at physiological pH, crystallises in the presence of an acidic pH. In newly diagnosed patients with an element of hyperleucostasis, acidic conditions may exist in a poorly perfused kidney and uric acid deposits then form particularly in the collecting ducts and ureters. The consequences are intraluminal tubular obstruction and oliguria of urate nephropathy.

Hyperphosphataemia is also implicated as a cause of acute renal failure. Lymphoblasts contain four times as much phosphate as normal lymphocytes [1]. Hyperphosphataemia has been found to be present in 31% of non-azotemic Burkitt's lymphoma patients and 100% of those with a raised urea level [1] and leads to hyperphosphaturia and hypocalcaemia. The hypocalcaemia probably results from tissue precipitation of calcium phosphate, but may also be due to inappropriately low plasma 1,25-dihydroxyvitamin D_3 levels [2]. The low levels of calcium induce increased parathyroid hormone levels which, in turn, causes decreased proximal reabsorption of phosphate. The increased urinary excretion of phosphate increases the risk for nephrocalcinosis or tubular obstruction from precipitation of calcium phosphate. Treating hypocalcaemia in a patient with hyperphosphataemia is an added risk factor and is accentuated when the urine is alkalinised, as this favours phosphate precipitation.

Renal failure may also be precipitated by one of the drugs used to prevent it. Allopurinol lowers uric acid production by inhibiting xanthine oxidase, which catalyses the conversion of hypoxanthine to xanthine and xanthine to uric acid (see Fig. 1). Consequently, the plasma levels of xanthine and hypoxanthine rise and are excreted in increased quantities in the urine. Xanthine may precipitate in a manner similar to uric acid, especially in alkaline urine, and may be a contributory factor in the pathogenesis of acute renal failure [6].

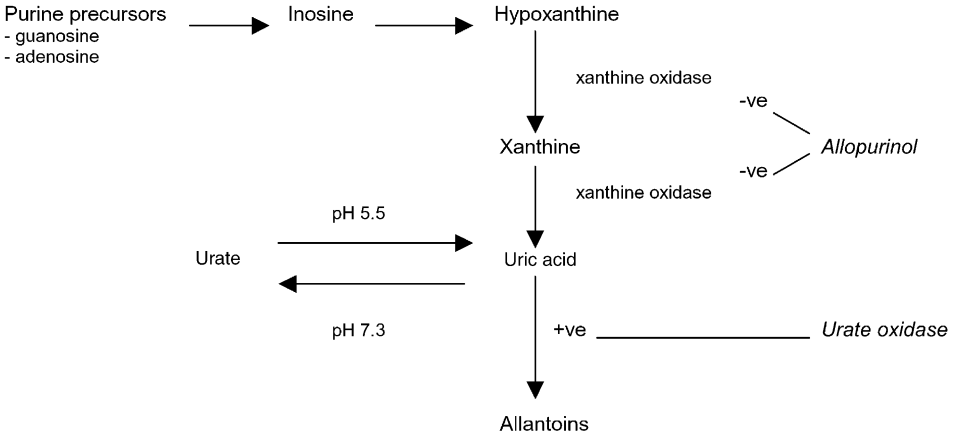

Fig. 1. Uric acid metabolism.

It is worth remembering that mechanisms other than tumour lysis syndrome may predispose to acute renal failure in a sick child with cancer. These include hypovolaemia from the fluid shifts associated with septicaemia or surgery, obstruction of the urinary tract or renal blood flow or direct infiltration of the kidneys by the tumour itself.

2.1.2. Clinical features

The clinical features of tumour lysis syndrome are summarised in Table 2.

2.1.3. Management

The ideal way to minimise the morbidity and mortality of tumour lysis syndrome is to anticipate and prevent it. All newly diagnosed children with cancer should have their plasma levels of urea, creatinine, sodium, potassium, calcium, phosphate, magnesium and urate measured to determine a baseline and detect any existing tumour lysis. In conditions where there is bulky abdominal disease, a renal ultrasound scan is indicated to anticipate renal infiltration by the tumour and hence a possible added risk of tumour lysis. Table 3 lists the manoeuvres employed routinely by most units to prevent and treat incipient tumour lysis syndrome.

The three basic tenets of tumour lysis syndrome prevention are hydration, alkalinisation of the urine and uric acid reduction. These measures should be utilised in all children prior to starting their first course of chemotherapy for acute lymphoblastic leukaemia or NHL (all types). Hydration should be started without delay at 3 l/m^2/day and increased if the serum potassium, phosphate or urate levels start to increase. To avoid fluid overload, urine output may need to be enhanced with the careful use of diuretics (to keep urine output $\geqslant 3$ ml/kg/h). It is usually necessary to monitor the blood biochemistry as frequently as 4 to 6 hourly. Alkalinisation of the urine to promote renal uric acid secretion, although widely advocated in medical texts, should be used with due caution. Excess alkalinisation may be hazardous as it may encourage precipitation of calcium phosphate and xanthine and lower the threshold for symptoms of hypocalcaemia [7,8]. If alkalinisation of the urine is practised, it should be discontinued when uric acid levels return to normal, in severe hyperphosphataemia or hypocalcaemia and certainly if symptomatic hypocalcaemia requires correction. Its use necessitates the frequent measurement of urinary pH and plasma bicarbonate levels (see Table 3). There are a number of units in the UK (author's personal experience) that do not routinely alkalinise the urine in any patients so there is a need for a randomised, controlled trial to determine the correct and safe practice.

Allopurinol is usually given orally although it is as safe and effective given intravenously (i.v.) [9]. Even with i.v. use, it has very few side-effects, but skin or allergic reactions can occur. An alternative medication is urate oxidase, a naturally occurring proteolytic enzyme that degrades uric acid to allantoins (see Fig. 1), which are 10 times more soluble than uric acid and easily eliminated by the kidneys. Unlike allopurinol, urate oxidase does not lead to the accumulation of xanthine and hypoxanthine. Mahmoud and colleagues [10] reviewed three large international studies performed in the UK, USA and France for the treatment of children with advanced stage B-cell NHL or ALL. The French study used urate oxidase and the other two used allopurinol. Although the chemotherapy regimens were not identical far fewer cases required dialysis in the French study compared with the other two. Pui and colleagues [11] have compared children with leukaemia-associated hyperuricaemia who were treated with urate oxidase against historical controls treated with allopurinol and concluded that urate oxidase caused a more rapid and greater decrease in the plasma uric acid, creatinine and urea. Urate oxidase is well tolerated with very few side-effects (allergic or anaphylactic reactions). It should be avoided, however, in patients with glucose-6-phosphate dehydrogenase deficiency. Urate oxidase is widely used in continental Europe and has recently been licensed for use in the UK. It is likely that it will become the drug of choice for the prevention and treatment of malignancy-associated hyperuricaemia.

Table 2
Clinical features of tumour lysis syndrome

Factor	Symptoms and signs
Hyperkalaemia	Paresthesias, weakness then flaccid paralysis. Gastrointestinal symptoms may occur. Arrhythmias and cardiac arrest ECG shows peaked T waves, lengthening of PR interval then widening of QRS complexes
Hyperuricaemia	Lethargy, nausea and vomiting
Hyperphosphataemia	Symptoms and signs usually related to resultant hypocalcaemia
Hypocalcaemia	Latent tetany may be demonstrated by Trousseau or Chovsteks signs Manifest tetany presents as carpopedal spasm, laryngospasm or convulsions ECG may show a prolonged QT interval
Acute renal failure	Oliguria or anuria, features of fluid overload—edema and hypertension

ECG, electrocardiogram.

Methods to reduce phosphate and potassium levels are listed in Table 3. Symptomatic hypocalcaemia, precipitated by hyperphosphataemia, can be a difficult problem to manage. It may be possible to avoid the situation by use of hydration fluids and prevention of hyperphosphataemia by use of oral aluminium hydroxide. However, for symptomatic hypocalcaemia, a slow bolus of 10% calcium gluconate 0.3–0.4 ml/kg over 5 to 10 min, with ECG monitoring, will rapidly alleviate the symptoms. Further management will depend on subsequent levels of phosphate, but the combination of symptomatic hypocalcaemia with hyperphosphataemia should provoke strong consideration for urgent renal dialysis.

Table 3
Methods to prevent or treat tumour lysis syndrome

Hydration	0.45% Saline with 5% dextrose, no added potassium, 3–6 l/m^2/day. Strict monitoring of intake and output Accurate measurements of weight once or twice daily may be useful, particularly in small children Keep urine specific gravity <1.010
Alkalinisation of urine (see text)	Add 50–100 mmol/l $NaHCO_3$ to hydration fluids Maintain urine pH at 7.0–7.5 Reduce $NaHCO_3$ if serum bicarbonate >30 mmol/l or urine pH >7.5 Use with caution if severe hyperphosphataemia orhypocalcaemia. Stop when uric acid levels return to normal or if patient requires correction of symptomatic hypocalcaemia
Uric acid reduction	Allopurinol 100 mg/m^2 every 8 h orally, or 150 mg/m^2 every 12 h over 30 min Reduce dose of allopurinol in established renal failure OR, urate oxidase 50–100 U/kg i.v.i. over 30 min or IM daily
Diuretics	Frusemide 0.5–1 mg/kg every 6 h slow i.v. bolus Mannitol 0.5 g/kg every 6 h i.v.i. over 30 min to maintain a good urine output ($\geqslant$3 ml/kg/h) and avoid fluid overload Avoid if hypovolaemia is present
Phosphate reduction	Aluminium hydroxide 50 mg/kg every 8 h orally
Potassium reduction	• Stop the intake of potassium-containing fluids and foods • Start potassium-binding resin Polystyrene sulphonate resin 0.25 g/kg every 6 h orally (exchanges 1–2 mmol of K^+/g of resin) • Consider i.v. frusemide if appropriate • Monitor ECG and if arrhythmia or significant widening of QRS complex, stabilise myocardium with: Calcium gluconate 10% 0.3–0.5 ml/kg slow i.v. bolus (5–10 min) with ECG monitoring to detect bradycardia • Potassium levels may be reduced rapidly in the short term by any of the following methods: 1 g/kg glucose i.v. with 0.25 U/kg insulin i.v. Salbutamol 2.5–5 mg nebulised or 4 μg/kg as a slow i.v. bolus (5 min) Bicarbonate 1–2 mmol/kg i.v. is useful if acidosis is present (dilute with 0.9% NaCl 1:10 if given peripherally or 1:5 if given centrally) • Consider dialysis
Symptomatic hypocalcaemia correction	Calcium gluconate 10% 0.3–0.5 ml/kg slow i.v. bolus (5–10 min) with ECG monitoring to detect bradycardia Only use if symptomatic because of risk of calcium phosphate precipitation Consider dialysis if severe
Dialysis and haemofiltration (see text)	• Indications for dialysis or haemofiltration: Hyperkalaemia Hyperuricaemia Hyperphosphataemia Symptomatic hypocalcaemia Uraemia High levels of creatinine Oliguria Volume overload Impending or continuing chemotherapy • Options available: Peritoneal dialysis Haemodialysis Continuous arteriovenous haemofiltration (CAVH) Continuous arteriovenous haemodiafiltration (CAVHD) Continuous venovenous haemofiltration (CVVH) Continuous venovenous haemodiafiltration (CVVHD)

i.v. = intravenously; i.v.i. = intravenous infusion; i.m. = intramuscularly.

All of the above manoeuvres may not be sufficient to maintain an adequate urine output or to keep control of the electrolyte levels. Dialysis or haemofiltration may then become necessary. The indications for dialysis differ between units and need to be individualised for each patient. It is prudent to discuss a child at high risk of tumour lysis syndrome with a paediatric renal unit before commencing chemotherapy and certainly at the first signs of evolving tumour lysis syndrome. An attempt may be made to correct electrolyte and urate levels, normalise acid-base balance and improve urine output before dialysis but once oliguria exists, dialysis will invariably be necessary. Peritoneal dialysis (PD), haemodialysis (HD) and continuous haemofiltration (arteriovenous and venovenous) with or without dialysis (CAVH, continuous arteriovenous haemofiltration; CAVHD, continuous arteriovenous haemodiafiltration; CVVH, continuous venovenous haemofiltration; CVVHD, continuous venovenous haemodiafiltration) have all been used successfully for the prevention and treatment of tumour lysis syndrome in children and adults [2,12–14]. Peritoneal dialysis used to be the modality of choice, but it is a risky procedure in potentially immunocompromised patients, particularly those with intra-abdominal tumour or postabdominal surgery. It is slower and less efficient at removing phosphate and correcting the fluid imbalances than other forms of dialysis. Haemodialysis has the advantage of being able to rapidly correct life-threatening hyperkalaemia and hypocalcaemia and rapidly reduces uric acid and phosphate levels. More than one treatment is usually required. There has been at least one report of large swings in plasma levels between treatments in a child who died of hyperkalaemia 6 h after a first cycle of haemodialysis [4]. Haemofiltration has been proposed in certain cases to supplement or replace haemodialysis. CAVH uses the patient's own arterial blood pressure to continuously filter blood via convective transport through a filter. CVVH utilises a blood pump to provide the filtration pressure obviating the need for arterial access. Both methods can be supported by instituting dialysis across the filter (CAVHD and CVVHD). Continuous haemofiltration is a gradual method of correcting fluid and electrolyte disturbances without imposing significant haemodynamic challenges on the child. It has been used after haemodialysis to cover the onset of chemotherapy or without haemodialysis in patients with evolving tumour lysis syndrome, but without life-threatening fluid overload or electrolyte imbalances.

2.2. Hypercalcaemia

Hypercalcaemia is usually defined as a serum calcium concentration greater than 3.24 mmol/l (13 mg/dl), which is a level usually associated with symptoms [20]. A newly diagnosed, unwell child may have a low serum albumin level and it is important to correct for this to avoid underestimating the significance of a measured calcium level. Although malignancy-associated hypercalcaemia is said to occur in up to 20% of adult cancers, it is rare in children. In a retrospective review of 6055 children with cancer treated at St Jude's Children's Research Hospital, only 25 (0.4%) were found to have hypercalcaemia [15]. It has been found in association most commonly with acute leukaemias and rhabdomyosarcomas (particularly alveolar histological subtype), but also malignant rhabdoid tumours of the kidney, Hodgkin's disease, NHL, hepatoblastoma, neuroblastoma, brain tumours and angiosarcoma [15,16]. The incidence of hypercalcaemia for each individual malignancy varies and is as high as 18% in children with renal rhabdoid tumours [17].

Hypercalcaemia has a number of possible causes. First, it may result from the release of calcium from sites of widespread bone metastases. Second, it may be caused by the production of tumour-derived humoral factors that cause generalised bone resorption including parathyroid hormone-related peptide (PTHrP), prostaglandin E_2 (PGE_2), tumour necrosis factor, interleukin-1 and transforming growth factor alpha [18,19]. The clinical features of hypercalcaemia include: muscle weakness, fatigue, nausea, vomiting, polyuria, abdominal or back pain and constipation. When severe, it can cause a depressed level of consciousness and bradyarrhythmias. An electrocardiogram (ECG) may show a prolonged PR interval and widened T waves. Symptoms in children may not be recognised because they are not specific and may be attributed to other problems.

Treatment aims at increasing the renal calcium clearance, inhibiting osteoclastic bone resorption and reducing or eliminating the tumour burden [20]. On diagnosis of hypercalcaemia, initial management is to increase i.v. fluid intake (3–6 l/m^2/day) and output with the concomitant use of high doses of frusemide (1–3 mg/kg every 6 h i.v.). This regime promotes the excretion of calcium and blocks its renal reabsorption. Careful monitoring of fluid balance and electrolytes is necessary and will suffice in mild to moderate hypercalcaemia. In some cases, however, further treatment will be necessary. Bisphosphonates are synthetic analogues of pyrophosphate that bind to hydroxyapatite crystals and inhibit resorption of bone by their action on osteoclasts. They have been used for years in adults with various conditions including hypercalcaemia of malignancy and, recently, successfully and safely in children [21,22]. They are probably the drugs of first choice in hypercalcaemia unresponsive to fluid and diuretics. Pamidronate is the bisphosphonate for which there is the most safety and efficacy data in childhood. It results in a predictable drop in calcium levels within 48 h. Adverse effects

include hypocalcaemia, hypophosphataemia and hypomagnesaemia. Young and colleagues recommend a dose of 1 mg/kg as an i.v. infusion (rate not >1 mg/min) with some patients requiring a further dose of 1 mg/kg [21].

If hypophosphataemia is also present, it may be useful to administer oral phosphate, although diarrhoea is often a troublesome side-effect. There is a danger of extra-osseous bone deposition—particularly if i.v. phosphate replacement is used. Other methods to control hypercalcaemia include the use of corticosteroids with or without calcitonin, mithramycin, indomethacin and gallium nitrate. Glucocorticoids have the advantage in lymphoproliferative disorders of reducing tumour load, as well as possibly reducing the production of some osteoclast stimulating factors. They have a slow and transient effect on calcium levels and have been used in conjunction with calcitonin. Mithramycin also inhibits osteoclasts, but it is also slow to drop calcium levels and has considerable toxicity. Indomethacin may be useful when PGE_2 is the major causative factor [19]. Dialysis may be required in cases that do not respond to the above medical measures.

3. Haematological problems

3.1. Hyperleucocytosis

Hyperleucocytosis, defined as a white cell count greater than 100×10^9/l, has been reported to occur in 5 to 20% of childhood leukaemias, and is more common in ALL than acute myeloid leukaemia (AML). Part of the increased morbidity and mortality attributed to hyperleucocytosis is related to the acute metabolic complications secondary to tumour lysis syndrome, but complications caused by stasis, particularly in the intracerebral and pulmonary circulations may pose separate, life-threatening complications.

Hyperleucocytosis results in increased viscosity, sludging of the circulation and white cell thrombi of small blood vessels. Ischaemia and haemorrhage may result. Clinical features of hyperleucostasis depend on the systems most affected. Pulmonary leucostasis may manifest initially with dyspnoea, tachypnoea and oxygen desaturation and progress to respiratory failure and death. Chest radiographs may be surprisingly normal or display diffuse interstitial infiltrates. Intracerebral clinical manifestations range from simple headaches or subtle behaviour changes to stroke or seizures with papilloedema and retinal vessel changes found on fundoscopy. Particularly, but not exclusively, in AML, hyperleucocytosis often precedes the onset of coagulopathy with resulting parenchymal haemorrhage (particularly intracranial). This complication has a very high morbidity and mortality rate [23] (see Section 3.2). Other reported complications include renal failure, cardiac failure, priapism and acute ischaemic changes in fingers, toes or limbs.

Initial management should include prompt administration of i.v. fluids, tumour lysis preventative methods (as this is often a co-existing danger) and early, careful introduction of chemotherapy, a judgement which requires an experienced clinician to balance the need for a rapid decrease in the white cell count and avoiding precipitating life-threatening tumour lysis syndrome. Basade and colleagues studied children with leukaemia presenting with leucocytosis, with total white blood cell (WBC) count $>100\times10^9$/l. They found the median reduction in white cell count using fluids, alkalinisation and allopurinol alone to be 81.5% (range 66 to 98.8%) within a median period of 36 h (range 12 to 60 h) [25]. It is important that thrombocytopenia and coagulation defects should be corrected because they increase the risk of bleeding. Red blood cell transfusions should be delayed and diuretics should be avoided if possible in the initial stages, because of the risk of further increasing blood viscosity. Starting appropriate chemotherapy will, in most cases, begin to reduce the WBC cell count within 48 h, although other manoeuvres such as leucapheresis and exchange transfusion have also been used successfully to temporarily lower the WBC count. Bunin and colleagues studied 12 children who underwent exchange transfusions and 23 who had leucaphereses [26]. They found these procedures equally effective (median decrease in peripheral leucocytes of 60%) and relatively safe, but there is little data on the effect of these procedures on the outcome of intracerebral or pulmonary complications, compared with chemotherapy. Although safe, they are not without risk, particularly because of the need for secure vascular access and anticoagulation. A trial comparing chemotherapy alone, with chemotherapy plus leucapheresis or exchange transfusion would be ideal but, in practice, few clinicians feel that the extra expense and risk of these procedures is justified.

3.2. Coagulopathy and acute haemorrhage

There are numerous reasons why a child being treated for cancer may suffer a serious, even life-threatening haemorrhage. Some of the causes are listed in Table 4. In some cases, several precipitants may co-exist. The bleeding in most of these cases may be controlled in the short term by the appropriate transfusion of platelets or coagulation factors (fresh frozen plasma or cryoprecipitate) plus attempts at local haemostasis (e.g. direct pressure onto a site of bleeding or the packing of a bleeding cavity). More definitive treatment will be required to correct the underlying cause of the bleeding—e.g. treatment of the underlying malignancy, antibiotics to control sepsis or administration of Vitamin K.

Table 5 summarises the different products and dosages required. Disseminated intravascular coagulopathy (DIC) secondary to acute promyelocytic leukaemia (APL/M3 variant of AML) is discussed here in more detail.

Coagulopathy at presentation or at the onset of induction treatment has been described with most types of acute leukaemia in children—particularly when associated with high white cell counts. It occurs in approximately 3% of cases of ALL [29], but more often with

Table 4
Causes of significant or life-threatening haemorrhage in children being treated for cancer

1. Thrombocytopenia
   - (a) Underproduction
     - (i) Bone marrow infiltration by acute leukaemia or other cancer[a]
     - (ii) Bone marrow suppression by chemotherapy[a]
   - (b) Increased consumption or destruction
     - (i) Sepsis/Pyrexia[a]
     - (ii) Thrombotic thrombocytopenic purpura (TTP)/Evans' syndrome post-bone marrow transplant
   - (c) Platelet sequestration
2. Coagulopathy
   - (a) Disseminated intravascular coagulopathy (DIC)[a]
     - (i) Secondary to infection
     - (ii) Release of procoagulant factors by acute promyelocytic leukaemia (APML/AML M3)
   - (b) Decreased production of coagulation factors
     - (i) Liver dysfunction/infiltration
     - (ii) Vitamin K deficiency
     - (iii) Asparaginase therapy (causes decreased fibrinogen levels, but more often causes thrombosis due to anti-coagulant (anti-thrombin III) deficiency)
3. Acquired von Willebrand disease
   - associated with Wilms' tumour
4. Mechanical/vascular factors
   - (a) Erosion of blood vessels by tumour
   - (b) Erosion of blood vessels by infection (e.g. *Aspergillus*)
   - (c) Complication of central venous lines

[a] Most likely causes.

Table 5
Products used in the treatment of severe haemorrhage

Product	Dose	Comments
Platelets	In children, a dose of 10–15 ml/kg should produce a therapeutic increment. 1 PC per 10 kg body weight will raise platelet level by 50×10^9/l. (PC = platelet concentrate = approximately 55×10^9 platelets/unit in 50 ml plasma. Platelets collected by apheresis will have a minimum of 3×10^{11}platelets in approximately 250 ml of plasma and an equivalent dose will be approximately 5 ml/kg) [27].	Indications [28]: • Platelet count $<10\times10^9$/l • Platelet count $<20\times10^9$/l and bone marrow infiltration, severe mucositis, DIC, anticoagulation therapy, a platelet count likely to fall below 10×10^9/l prior to next evaluation, or risk of bleeding due to local tumour invasion • Platelet count <30–40×10^9/l and DIC (e.g. during induction therapy forAPL), extreme hyperleucocytosis, or prior to lumbar puncture or central venous line insertion • Platelet count <50–60×10^9/l and major surgical intervention
Fresh frozen plasma (FFP)	10–15 ml/kg i.v.i.	Provides procoagulant proteins and inhibitors
Cryoprecipitate	10 ml/kg i.v.i.	Provides higher concentration of fibrinogen and F VIII. Should be used specifically when the fibrinogen level is low. Aim to keep fibrinogen levels >1 g/l
Vitamin K	4 wks–1 yr: 300 mcg/kg 1–4 yr: 3 mg 5–12 yr: 5 mg $>$ 12 yr: 10 mg given as an intravenous infusion over 15 min	For the child with significant haemorrhage and where Vitamin K deficiency or liver dysfunction is thought to play a role. In the emergency situation is probably best given intravenously, with an anticipated effect at 3–6 h postadministration.

In cases of severe haemorrhage, the use of anti-fibrinolytics and heparin is controversial and should only be used after discussion with a paediatric haematologist.
wks, weeks; yr, year; F, factor, h, hours.

AML—in 13–17% of cases at presentation [30], particularly in subtypes M3, M4 and M5. In the M3 variant—acute promyelocytic leukaemia (APL), bleeding can be life-threatening and occur at presentation or just after the onset of chemotherapy. Various mechanisms for the DIC have been postulated [31] including: the release of thromboplastins and other procoagulant tissue factors from the myoblast granules; excessive fibrinolysis due to release of plasminogen activator or direct fibrinogen breakdown by proteases or endothelial cell-derived interleukin-1 [32]. Coagulopathy has been the main cause of induction deaths in APL despite the availability of platelets and the use of heparin and antifibrinolytics, but has improved in recent years with the widespread use of all-*trans* retinoic acid (ATRA). ATRA induces terminal differentiation of malignant myeloid cells to mature neutrophils, and its side-effects are well tolerated in childhood. It does not eradicate the malignant myeloid clone in APL and needs to be combined with conventional chemotherapy to cure the patient. However, ATRA has been shown to rapidly ameliorate the coagulopathy of APL [32,33], reduce the severity of bleeding symptoms and decrease blood product consumption [34]. Despite this, large trials have not consistently shown a significant reduction in early haemorrhagic deaths [34–36]. The main side-effects of ATRA in children are an increase in white cell count and the ''ATRA syndrome'', characterised by fever, respiratory distress, weight gain and headache.

All children with newly diagnosed leukaemia should have their coagulation status tested at diagnosis and abnormalities should be corrected promptly. Significant coagulopathy should be anticipated in those with very high white cell counts and particularly in the M3, M4 and M5 variants of AML. In APL, ATRA should be started with the onset of chemotherapy and coagulation tests should be performed regularly. Platelet counts should be kept above $30–40\times10^9$/l. In established coagulopathy, platelets, FFP and cryoprecipitate should be given according to the guidelines in Table 5.

4. Space-occupying tumour problems

4.1. Superior vena cava syndrome

Most childhood cases of superior vena cava syndrome arise due to compression caused by an anterior mediastinal tumour, middle mediastinal lymph nodes or acute thrombosis of the superior vena cava (SVC). As its name implies, it involves compression or obstruction of the SVC, but the underlying pathology may also cause pressure on the trachea, larger airways and pulmonary vessels. It should perhaps be more appropriately termed ''Superior Mediastinal Syndrome'' or ''Anterior Mediastinal Mass Syndrome''.

Superior vena cava syndrome is most commonly caused by lymphoid malignancy—NHL (mostly lymphoblastic or large cell histological types), ALL (especially T-cell ALL) and Hodgkin's disease. However, germ cell tumours, thyroid cancer, thymoma, neuroblastoma, rhabdomyosarcoma and Ewing's sarcoma have also been reported [37]. With the increasing use of indwelling central venous catheters, SVC thrombosis is emerging as another cause of SVC syndrome.

4.1.1. Clinical presentation

Clinical presentation is variable and may develop gradually or unexpectedly. SVC obstruction decreases venous return to the heart and increases venous pressure in the head, neck and upper thorax. Symptoms include facial swelling, orthopnoea, dyspnoea, cough, chest pain, headaches, dizziness, syncope and episodes of confusion or anxiety. Examination may reveal facial oedema and plethora, cyanosis and distended veins on the head and upper body. Pulsus paradoxus, hypertension and papilloedema may be present. Airway compression can cause wheeze, diminished breath sounds and decreased arterial oxygen saturations. Some of these symptoms and signs may be worse or only elicited when the child is in the supine position. General anaesthesia is also hazardous with tracheal or bronchial obstruction occurring at any time: during induction, intubation, positioning or extubation. Profound hypoxaemia may occur from compression of the great vessels despite patent airways [38].

4.1.2. Investigation of a child with suspected superior vena cava syndrome

Inappropriate investigations and management may introduce further hazards. Sedation, anaesthesia or even the supine position for imaging may precipitate rapid decompensation and a sudden cardio-respiratory arrest [39–42]. The diagnosis should therefore be established by the least invasive means possible. In some cases, empirical anti-cancer therapy may need to be started without a histological diagnosis, but with planned attempts to obtain histological samples as soon as the patient's clinical status improves.

Erect posteroanterior and lateral chest X-rays will reveal widening of the mediastinum and may distinguish between a solid anterior mediastinal mass and middle mediastinal nodes. Pleural effusions may be present and an enlarged heart shadow may suggest a pericardial effusion. It is unnecessary in most cases to perform further imaging at this stage, however, if it is performed it should only be done without sedation, with adequate monitoring and if feasible carried out in the prone or lateral position. Other investigations may reveal enough information to make a clinical diagnosis. A full blood count and film may reveal evidence of leukaemia. Blood biochemistry may show evidence of a high

tumour load with a raised urea and creatinine, potassium, phosphate, urate and lactate dehydrogenase (LDH). Tumour markers are usually elevated in patients with germ cell tumours and raised urinary catecholamine metabolite levels will be diagnostic of a neuroblastoma. A bone marrow biopsy, pleural or pericardial aspiration or lymph node biopsy may be done safely with local anaesthetic in a co-operative child in the upright or lateral position and will often yield a diagnosis.

If the diagnosis is still not clear after these procedures (27% of cases in one large series [38]), a decision needs to be made between more invasive investigations performed under general anaesthetic or starting empirical chemotherapy or radiotherapy. Current treatment protocols are usually cell type-specific and incorporate risk stratification approaches, so it is important to have an accurate diagnosis of tumour cell type. Concern has been raised that in patients without a tissue diagnosis, pre-operative treatment may mask the diagnosis. Many childhood tumours (especially the haematological malignancies) are extremely chemosensitive and shrink rapidly following the start of treatment with consequent distortion or loss of the histopathology [43]. The same applies to radiotherapy [44].

Attempts have been made to identify tests predictive of anaesthesia-related problems in these children. Orthopnoea is the only clinical feature traditionally associated with respiratory collapse. Reports have suggested that tracheal cross-sectional area obtained from computerised tomography (CT) scans and pulmonary function tests may provide additional information about the anaesthetic risk [39,45,46]. However, the dangers of performing a CT scan in these circumstances are considerable. Flow-volume loops and peak expiratory flow rates (PEFRs) have been evaluated in children with intrathoracic airways obstruction [45,46]. Of these two procedures, PEFRs are relatively simple to perform in the co-operative child and are a good reflection of central airway size. Shamberger and colleagues [45] report that children with tracheal cross-sectional areas measuring $>50\%$ and a PEFR of $>50\%$ of the predicted normal values tolerate general anaesthetic well. Impairment of venous return and cardiac compromise may be assessed by an ECG and echocardiography.

Ferrari and Bedford reported their experience of 163 consecutive children with anterior mediastinal masses, of whom 44 underwent a surgical diagnostic procedure requiring general anaesthesia prior to treatment [38]. 9 of these 44 patients were symptomatic and 5 had features of SVC syndrome. 7 (16%), 5 of whom were symptomatic pre-anaesthetic, developed potentially life-threatening airway compromise at least once in the peri-anaesthetic period. All 7 patients survived without sequelae, although 3 required chemotherapy or radiotherapy prior to successful extubation. The authors concluded, controversially, that in the absence of life-threatening preoperative airway obstruction and severe clinical symptoms, general anaesthesia may be safely induced prior to radiation therapy. They recommended, however, that general anaesthesia should only be carried out under certain circumstances: spontaneous ventilation should be preserved whenever possible, induction should proceed with the patient in the sitting position, i.v. access should be secured in the lower extremity, it must be possible to rapidly alter the patient's position whenever cardiorespiratory compromise becomes apparent, a functioning rigid bronchoscope and a skilled bronchoscopist should be readily available and the possibility of emergency cardiopulmonary bypass must be considered. Only the largest specialist centres will be able to muster these resources and although Ferrari and Bedford illustrate what can be achieved under ideal settings, an incidence of 16% life-threatening airway compromise cannot allow their approach to be generally recommended. If a general anaesthetic is performed, tissue for histology can usually be successfully obtained from a lymph node biopsy, CT or ultrasound-guided percutaneous biopsy or via mediastinoscopy.

4.1.3. Empirical treatment of a child with superior vena cava syndrome

If a general anaesthetic is not considered safe and diagnostic material cannot be obtained under local anaesthetic, then immediate empirical therapy to alleviate the SVC syndrome might be appropriate prior to any further invasive investigations. In this case, the patient must be assessed frequently for improvement and a biopsy performed as soon as practically possible. Inevitably this approach will lead to a small number of children in whom a definitive diagnosis is never reached, and these patients will have to be treated for the most likely diagnosis. It is preferable, after all, to have a live patient without a diagnosis than a diagnosed, but dead child!

For the suspected haematological malignancies (ALL, NHL and Hodgkin's disease) and for some of the solid tumours, chemotherapy, including steroids, is often rapidly effective and would be the treatment of first choice in children. Radiotherapy has previously always been the mainstay of treatment [47] for empirical treatment and may continue to play a role in some cases.

4.2. Spinal cord compression

Spinal cord compression is uncommon in childhood. Urgent investigation and management are required to minimise neurological damage. In a study of 2259 children with solid malignant tumours treated between 1962 and 1987, 5% developed spinal epidural compression

during their disease course [48]. Lewis and colleagues found a similar incidence of 4% in a study of 643 solid and 'lymphoreticular' malignancies [49]. Although it is most common in the terminal phases of widespread metastatic malignancy, some 25–35% of cases occur as the initial presenting complaint [49,50], usually due to extension of a paravertebral neuroblastoma or Ewing's sarcoma (PNET) through one or more intravertebral foramina causing epidural compression, the so-called "dumb-bell tumour". The extending tumour causes compression of the vertebral venous plexus leading to vasogenic oedema, venous haemorrhage, demyelination and ischaemic cell death [51]. Other tumours associated with spinal cord compression in children are listed in Table 6. A picture similar to spinal cord compression may have other causes in children with cancer. Lewis and colleagues reported that 12% of their patients had other causes for their symptoms including infection, radiation myelopathy, spinal cord infarction and intraspinal haematomas secondary to a coagulation problem [14].

4.2.1. Clinical presentation of spinal cord compression in children

Table 7 lists the common presenting features of spinal cord compression in children.

Back pain is an otherwise uncommon complaint in children and should be investigated promptly. Urgency is increased if a neurological deficit is detected as paraplegia or quadriplegia can evolve within hours [52]. Unfortunately, the mean duration of symptoms before diagnosis is commonly reported to be as long as 4–8 weeks [50,53]. Plain spine radiographs in children are only abnormal in approximately a third of cases [49]. MRI is the current initial investigation of choice [54,55]. Apart from the need to administer sedation or general anaesthetic to small children, it is non-invasive and gives high-quality images of the spinal cord, epidural space and paravertebral areas. CT scans, preferably with contrast, will give enough information to facilitate emergency referral to a neurosurgical centre. Myelography should only be performed when neither MRI nor CT scanning are available [24].

Table 6
Incidences of spinal cord compression (SCC) in children

Pathology	Causes of SCC (% of all cases)	Incidence of SCC per tumour type (%)
References	[37–39]	[38]
Neuroblastoma	27	7.9
Ewing's sarcoma	23	17.9
Rhabdomyosarcoma	15	4.9
Osteosarcoma	12	6.5
Other soft-tissue sarcoma	7	3.9
Hodgkin's disease	5	2.0
Germ cell tumour	4	3.8
Non-Hodgkin's lymphoma or leukaemia	3	
Wilms' tumour	2	0.7
Other	1	1.4

Table 7
Presenting features of spinal cord compression in children

Clinical feature	Percentage of patients	Comment
References	[38,39]	
Back pain • localised or radicular	61–80	Most common presenting symptom—may precede other features
Weakness • ambulatory • non-ambulatory • paraplegic	67–82 55 33 12–57	Most common clinical sign
Localised spine tenderness	67	
Sphincter disturbances • usually urinary retention or constipation	51–57	
Sensory disturbances • paresthesias or dysesthesias	14–52	Sensory level difficult to assess accurately in small, non-verbal children
Gait disturbances	8	

Investigations that may be helpful in determining the nature of the spinal tumour and also aid in deciding on the correct treatment include: urinary catecholamine metabolites (pointing towards a neuroblastoma), full blood count and film (may provide clues to an underlying leukaemia or NHL) and germ cell tumour markers.

4.2.2. Management

Standard emergency treatment is to administer 1 mg/kg of i.v. dexamethasone (over 30 min) [24,49,56,57], before or immediately after urgent imaging. A lower dose of 0.25 to 0.5 mg/kg orally 6 hourly has been advocated for cases without neurological deficits whilst an MRI is awaited [24]. If a cord-compressing space-occupying lesion is confirmed, a decision between immediate surgical decompression vs. radiotherapy or chemotherapy has to be made. This decision will be influenced by a number of factors, principally: (a) the availability of a histological diagnosis; (b) the anticipated response of the specific tumour type to radiotherapy or chemotherapy; (c) the extent of neurological deficit and (d) the speed of its progression. The immediate goal is to restore neurological function.

If there is no histological diagnosis or a diagnosis cannot be made rapidly by other means, surgery will often be required immediately. A multi-level posterior laminectomy is often performed but can lead to later problems with subluxation, scoliosis and kyphosis [58,59] and most long-term survivors will require further reconstructive spinal treatment [59]. Many surgeons are now performing osteoplastic laminotomies instead of laminectomy, followed by bracing for 6–8 weeks. It is likely, but not yet known, whether the long-term incidence of deformities will be less with this procedure. Spinal radiotherapy also causes late scoliosis and kyphosis—particularly in very young children, those receiving asymmetrical spine irradiation and radiation greater than 2000 cGy [59,60]. Chemotherapy, used as the initial therapy, has the advantage of not only avoiding these long-term deformities, but also gaining control of the cancer at the primary or other metastatic sites without a delay. There are a number of reports indicating that chemotherapy is effective in relieving pressure on the spinal cord with long-term neurological outcome at least as good as surgery or radiotherapy [56,61–63]. In a prospective study by the French Society of Pediatric Oncology, children with non-metastatic neuroblastomas and intraspinal extension were treated according to specific guidelines [62]. Neurosurgical decompression was recommended only for patients with rapid neurological deterioration or if paraplegia had evolved within 72 h of presentation. Of the 27 patients with neurological impairment, 6 underwent a neurosurgical procedure initially and 5 made a complete neurological recovery. Of the 19 who received primary chemotherapy evaluable for functional outcome, 12 had a complete recovery, 3 had partial recovery and 4 failed to recover.

Of course, the ultimate outcome for these children depends on the extent of the cancer at diagnosis and the response to treatment, but their ultimate "quality of life" depends on the long-term neurological sequelae. Effective team work and carefully planned and decisive action is the key to the best outcome for these children.

Acknowledgements

I would like to thank Chris Mitchell for kindly making time to read and correct the draft of this article. Thanks are also due to Jeff Elliott, our departmental Paediatric Oncology Pharmacist, for checking the drug dosages.

References

1. Cohen LF, Balow JE, Magrath IT, Poplack DG, Ziegler JL. Acute tumor lysis syndrome: a review of 37 patients with Burkitt's lymphoma. *Am J Med* 1980, **68**, 486–491.
2. Jones DP, Mahmoud H, Chesney RW. Tumor lysis syndrome: pathogenesis and management. *Pediatr Nephrol* 1995, **9**, 206–212.
3. Griffen TC, Bowman P, Winick NJ, Buchanan GR. Treatment of advanced stage diffuse, small non-cleaved cell lymphoma in childhood: further experience with total therapy. *Med Pediatr Oncol* 1994, **23**, 393–399.
4. Stapleton FB, Strother DR, Roy S, Wyatt RJ, McKay CP, Murphy SB. Acute renal failure at onset of therapy for advanced stage Burkitt lymphoma and B cell acute lymphoblastic lymphoma. *Pediatrics* 1988, **82**, 863–869.
5. Rieselbach RE, Bentzel CJ, Cotlove E, Frei E, Freirich EJ. Uric acid excretion and renal function in the acute hyperuricemia of leukemia: pathogenesis and therapy of uric acid nephropathy. *Am J Med* 1964, **37**, 872–884.
6. Andreoli SP, Clark JH, McGuire WA, Bergstein JM. Purine excretion during tumor lysis in children with acute lymphocytic leukemia receiving allopurinol: relationship to acute renal failure. *J Pediatr* 1986, **109**, 292–298.
7. Veenstra J, Krediet RT, Somers R, *et al*. Tumour lysis syndrome and acute renal failure in Burkitt's lymphoma. Description of 2 cases and a review of the literature on prevention and management. *Neth J Med* 1994, **45**, 211–216.
8. Ten Harkel ADJ, Kist-Van Holthe JE, van Weel M, *et al*. Alkalinization and the tumor lysis syndrome. *Med Ped Oncol* 1998, **31**, 27–28.
9. Smalley RV, Guaspari A, Haase-Statz S, Anderson SA, Cederberg D, Hohneker JA. Allopurinol: intravenous use for prevention and treatment of hyperuricaemia. *J Clin Oncol* 2000, **18**, 1758–1763.
10. Mahmoud HH, Leverger G, Patte C, Harvey E, Lascombes F. Advances in the management of malignancy-associated hyperuricaemia. *Br J Cancer* 1998, **77**(Suppl. 4), 18–20.
11. Pui CH, Relling MV, Lascombes F, *et al*. Urate oxidase in prevention and treatment of hyperuricaemia associated with lymphoid malignancies. *Leukemia* 1997, **11**, 1813–1816.
12. Deger GE, Wagoner RD. Peritoneal dialysis in acute uric acid nephropathy. *Mayo Clin Proc* 1972, **47**, 189–192.

13. Heney D, Essex-Cater A, Brocklebank JT, Bailey CC, Lewis IJ. Continuous arteriovenous haemofiltration in the treatment of tumour lysis syndrome. *Pediatr Nephrol* 1990, **4**, 245–247.
14. Saccente SL, Kohaut EC, Berkow RL. Prevention of tumor lysis syndrome using continuous veno-venous haemofiltration. *Pediatr Nephrol* 1995, **9**, 569–573.
15. McKay C, Furman WL. Hypercalcemia complicating childhood malignancies. *Cancer* 1993, **72**, 256–260.
16. LeBlanc A, Caillaud JM, Hartmann O, *et al*. Hypercalcemia preferentially occurs in unusual forms of childhood non-Hodgkin's lymphoma, rhabdomyosarcoma, and Wilms' tumor. *Cancer* 1984, **54**, 2132–2136.
17. Vujanic GM, Sandstedt B, Harms D, Boccon-Gibod L, Delemarre JF. Rhabdoid tumour of the kidney: a clinicopathological study of 22 patients from the International Society of Paediatric Oncology (SIOP) nephroblastoma file. *Histopathology* 1996, **28**, 333–340.
18. Ralston S. Pathogenesis of humoral hypercalcaemia of malignancy. *Lancet* 1987, **ii**, 1443–1445.
19. Mitchell CD, Harvey W, Gordon D, Womer RB, Dillon MJ, Pritchard J. Rhabdoid Wilms' tumour and prostaglandin-mediated hypercalcaemia. *Eur Paediatr Haematol Oncol* 1985, **2**, 153–157.
20. Ritch PS. Treatment of cancer-related hypercalcaemia. *Semin Oncol* 1990, **17**(Suppl. 5), 26–33.
21. Young G, Shende A. Use of pamidronate in the management of acute cancer-related hypercalcemia in children. *Med Pediatr Oncol* 1998, **30**, 117–121.
22. Srivastava T, Alon US. Bisphosphonates: from grandparents to grandchildren. *Clin Pediatr Phila* 1999, **38**, 687–702.
23. Wurthner JU, Kohler G, Behringer D, Lindemann A, *et al*. Leukostasis followed by hemorrhage complicating the initiation of chemotherapy in patients with acute myeloid leukemia and hyperleukocytosis: a clinicopathologic report of four cases. *Cancer* 1999, **85**, 368–374.
24. Kelly KM, Lange B. Oncologic emergencies. *Pediatric Clinics of North America* 1997, **44**, 809–830.
25. Basade M, Dhar AK, Kulkarni SS, *et al*. Rapid cytoreduction in childhood leukemic hyperleukocytosis by conservative therapy. *Med Pediatr Oncol* 1995, **25**, 204–207.
26. Bunin NJ, Kunkel K, Callihan TR. Cytoreductive procedures in the early management in cases of leukemia and hyperleukocytosis in children. *Med Pediatr Oncol* 1987, **15**, 232–235.
27. Hume HA. Transfusion support of children with hematologic and oncologic disorders. In Petz LD, Swisher SN, Kleinmans R, Spence RIC, Strauss RG, eds. *Clinical Practice of Transfusion Medicine,* 3rd edn. New York, Churchill Livingstone, 1996, 705–732.
28. Hume HA. Blood components: preparation, indications and administration. In Lilleyman J, Hann I, Blanchette V, eds. *Pediatric Hematology,* 2nd edn. London, Churchill Livingstone, 1999, 709–740.
29. Ribeiro RC, Pui CH. The clinical and biological correlates of coagulopathy in children with acute leukemia. *J Clin Oncol* 1986, **4**, 1212–1218.
30. Pui CH, Behm FG. Pathology of acute myeloid leukemia. In Lilleyman J, Hann I, Blanchette V, eds. *Pediatric Hematology,* 2nd edn. London, Churchill Livingstone, 1999, 369–385.
31. Tallman MS, Hakiman D, Kwaan HC, Rickles FR. New insights into the pathogenesis of coagulation dysfunction in acute promyelocytic leukemia. *Leuk Lymphoma* 1993, **11**, 27–36.
32. Bapna A, Nair R, Tapan KS, *et al*. All-trans retinoic acid (ATRA): pediatric acute promyelocytic leukemia. *Pediatr Hematol Oncol* 1998, **15**, 243–248.
33. Dompret H, Scroboaci ML, Ghorra P, *et al*. Coagulation disorders associated with acute promyelocytic leukemia: corrective effect of all-trans retinoic acid. *Leukemia* 1993, **7**, 2–9.
34. Di Bona E, Avvisati G, Castaman G, *et al*. Early haemorrhagic morbidity and mortality during remission induction with or without all-trans retinoic acid in acute promyelocytic leukemia. *Br J Haematol* 2000, **108**, 689–695.
35. Fenaux P, Le Deley MC, Castaigne S, *et al*. Effect of all-*trans* retinoic acid in newly diagnosed acute promyelocytic leukemia. Results of a multicenter randomized trial. *Blood* 1993, **82**, 3241–3249.
36. Tallman MS, Andersen JW, Shiffer CA, *et al*. All-trans retinoic acid in acute promyelocytic leukemia. *NEJM* 1997, **337**, 1021–1028.
37. King RM, Telander RL, Smithson WA, Banks PM, Han M-T. Primary mediastinal tumors in children. *J Pediatr Surg* 1982, **17**, 512–520.
38. Ferrari LR, Bedford RF. General anesthesia prior to treatment of anterior mediastinal masses in pediatric cancer patients. *Anesthesiology* 1990, **72**, 991–995.
39. Azizkhan RG, Dudgeon DL, Buck JR, *et al*. Life threatening airway obstruction as a complication to the management of mediastinal masses in children. *J Pediatr Surg* 1985, **20**, 816–822.
40. Bittar D. Respiratory obstruction associated with induction of general anesthesia in a patient with mediastinal Hodgkin's disease. *Anesth Analg* 1975, **54**, 399–403.
41. Northrip D, Bohman B, Tuesada K. Total airway occlusion and superior vena cava syndrome in a child with anterior mediastinal tumor. *Anesth Analg* 1986, **65**, 1079–1082.
42. Levin H, Bursztein S, Heifetz M. Cardiac arrest in a child with an anterior mediastinal mass. *Anesth Analg* 1985, **64**, 1129–1130.
43. Halpern S, Chatten J, Meadows AT, *et al*. Anterior mediastinal masses : anesthesia hazards and other problems. *J Pediatr* 1983, **102**, 407.
44. Loeffler JS, Leopold KA, Recht A, *et al*. Emergency prebiopsy radiation for mediastinal masses: impact on subsequent pathologic diagnosis and outcome. *J Clin Oncol* 1986, **4**, 716.
45. Shamberger RC, Holzman RS, Griscom NT, Tarbell NJ, Weinstein HJ, Wold ME. CT quantitation of tracheal cross-sectional area as a guide to the surgical and anesthetic management of children with anterior mediastinal masses. *J Pediatr Surg* 1991, **26**, 138–142.
46. Miller RD, Hyatt RE. Evaluation of obstructing lesions of the trachea and larynx by flow-volume loops. *Am Rev Respir Dis* 1973, **108**, 475–481.
47. Piro A, Weiss D, Hellman S. A possible danger for intubation anesthesia. *Int J Radiat Oncol Bio Phys* 1976, **1**, 415–419.
48. Klein SL, Sanford RA, Mulbauer MS. Pediatric spinal epidural metastases. *J Neurosurg* 1991, **74**, 70–75.
49. Lewis DW, Packer RJ, Raney B, Rak IW, Belasco J, Lange B. Incidence, presentation and outcome of spinal cord disease in children with systemic cancer. *Pediatrics* 1986, **78**, 438–443.
50. Raffel C, Neave VCD, Lavine S, McComb JG. Treatment of spinal cord compression by epidural malignancy in childhood. *Neurosurgery* 1991, **28**, 349–352.
51. Manabe S, Tanaka H, Higo Y, *et al*. Experimental analysis of the spinal cord compressed by spinal metastasis. *Spine* 1989, **14**, 1308.
52. Byrne TN. Spinal cord compression from epidural metastases. *N Engl J Med* 1992, **327**, 614.
53. Conrad EU, Olszewski AD, Berger M, Powell E, Bruckner J. Pediatric spine tumors with spinal cord compromise. *J Pediatr Orthop* 1992, **12**, 454–460.
54. Carmody RF, Yang PJ, Seeley GW, *et al*. Spinal cord compression due to metastatic disease: diagnosis with MR imaging versus myelography. *Radiology* 1989, **173**, 225.
55. Smoker WRK, Godersky JC, Knutzon RK, *et al*. The role of MR imaging in evaluating metastatic spinal disease. *Am J Roentgenol* 1987, **149**, 1241.
56. Sanderson IR, Pritchard J, Marsh HT. Chemotherapy as the initial treatment of spinal cord compression due to disseminated neuroblastoma. *J Neurosurg* 1989, **70**, 688–690.

57. Delattre JY, Arbit E, Thaler HT, *et al*. A dose-response study of dexamethasone in a model of spinal cord compression caused by epidural tumor. *J Neurosurg* 1989, **70**, 920.
58. Raimondi AJ, Gutierrez FA, Di Rocco C. Laminotomy and total reconstruction of the posterior spinal arch for spinal canal surgery in childhood. *J Neurosurg* 1976, **45**, 555–560.
59. Mayfield JK, Riseborough EJ, Jaffe N, *et al*. Spinal deformity in children treated for neuroblastoma. The effect of radiation and other forms of treatment. *J Bone Joint Surg (Am)* 1981, **63**, 183–193.
60. Riseborough EJ, Grabias SL, Burton RI, *et al*. Skeletal alterations following irradiation for Wilm's tumor. *J Bone Joint Surg (Am)* 1976, **58**, 526–536.
61. Hoover M, Bowman LC, Crawford SE, *et al*. Long-term outcome of patients with intraspinal neuroblastoma. *Med Pediatr Oncol* 1999, **32**, 353–359.
62. Plantaz D, Rubie H, Michon J, *et al*. The treatment of neuroblastoma with intraspinal extension with chemotherapy followed by surgical removal of residual disease. *Cancer* 1996, **78**, 311–319.
63. Hayes FA, Thompson FI, Hvizdala E, *et al*. Chemotherapy as an alternative to laminectomy and radiation in the management of epidural tumor. *J Pediatr* 1981, **104**, 221–224.